# PRODUCTION OF RADIOISOTOPES OF MEDICAL INTEREST BY PHOTONUCLEAR REACTION USING ELI–NP $\gamma$-RAY BEAM*

Wen Luo[a,b†], Mariana Bobeica[a], Dan Filipescu[a]
Ioana Gheorghe[a,c], Dana Niculae[a], Dimiter L. Balabanski[a]

[a]Extreme Light Infrastructure — Nuclear Physics (ELI–NP)/
"Horia Hulubei" National Institute
for R&D in Physics and Nuclear Engineering (IFIN-HH)
30 Reactorului St., Bucharest-Măgurele
jud. Ilfov, P.O.B. MG-6, RO-077125, Romania
[b]School of Nuclear Science and Technology, University of South China
421001 Hengyang, China
[c]Faculty of Physics, University of Bucharest, 077125, Bucharest, Romania

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The radioisotope production has a crucial role in medical diagnosis and therapy. In this work, we investigated the possibility of obtaining radioisotopes of medical interest through photo-neutron reactions using the high-intensity $\gamma$ beams at the Extreme Light Infrastructure — Nuclear Physics (ELI–NP) facility. The specific activity for three benchmark radioisotopes, $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac, was obtained as a function of $\gamma$-beam energy, target geometry and irradiation time. Optimization for the generation of these radioisotopes at ELI–NP was investigated. We estimated that a saturation specific activity of the order of 1–2 mCi/g could be obtained for a thin target (radius 1–2 mm, thickness 1 cm) and for a conservative $\gamma$-beam flux of $10^{11}$ s$^{-1}$. The ELI–NP, based on these estimations, could provide the possibility for the production of certain radioisotopes in sufficient quantities for nuclear medicine research.

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## 1. Introduction

Radioisotopes are used in industry, research, and nuclear medicine. One of the most important application is nuclear medicine, where radioisotopes are used for diagnostic and therapeutic purposes. Over 10,000 hospitals

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† Corresponding author: wenluo-ok@163.com

worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis. The global radioisotope market was valued at $4.8 billion in 2012, with medical radioisotopes accounting for about 80% of this, and is poised to reach about $8 billion by 2017 [1].

Currently, thermal neutron-induced fission and charged-particle reactions with protons are the main production routes for medical radioisotopes. Unfortunately, both production techniques have a number of disadvantages, since they need nuclear reactors and cyclotrons. Nuclear reactors have produced a wide range of radioisotopes, but their shutdowns have caused global shortages of $^{99}$Mo/$^{99m}$Tc radioisotope. Further, the reactors led to large amount of nuclear waste, raising numerous safety and security concerns. Cyclotrons may not pose such risks compared to reactors, but they produce only a limited range of isotopes for clinical use.

The interest in using the high-intensity $\gamma$ beam for radioisotopes production lies in the possibility to obtain high specific activity for radioisotopes that are not produced currently in enough quantity, and also for extending the range of potentially useful clinical isotopes. Photon-induced reactions have been studied to be a robust mean of production of neutron-deficient isotopes [2], but conventional bremsstrahlung photon beam sources do not have a flux density sufficiently high to produce radioisotopes with high enough specific activities. In contrast to conventional bremsstrahlung photon beam sources, Compton backscattering (CBS) $\gamma$-beam sources provide the capability to selectively tune photons to energies of interest [3–5]. This feature, coupled with the ubiquitous giant dipole resonance excitations of atomic nuclei, promises a fertile method for production of radioisotopes of medical interest [6].

The large scale facility Extreme Light Infrastructure — Nuclear Physics (ELI–NP) [7], currently under development, is the one of the three pillars of the Extreme Light Infrastructure Pan-European initiative which is dedicated to nuclear physics with extreme electromagnetic fields. Two 10 PW lasers and one very brilliant $\gamma$-beam facility will be installed at ELI–NP. The $\gamma$-beam facility will produce highly polarized ($> 95\%$), CBS-based tunable $\gamma$-ray beams of spectral density of $10^4$ photons/s/eV in the range from 200 keV to 19.5 MeV with a bandwidth of $\leq 0.5\%$. This will likely allow to produce certain radioisotopes useful for medical diagnostics and radiotherapy. With these considerations, we investigated the possibility of producing radioisotopes of medical interest through photo-neutron reactions using the high-intensity ELI–NP $\gamma$ beams.

## 2. Selection of radioisotopes of medical interest

In this paper, we selected three production cases, $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac to investigate the potential of production of medical radioisotopes at ELI–NP. $^{99}$Mo/$^{99m}$Tc was chosen because of its well-known $(\gamma, n)$ cross section [8]. While other facilities do have potential capabilities to decrease the gap between demand and supply chain, $^{99m}$Tc will be considered for testing the new production method and as a standard at ELI–NP, since its separation processes and the associated technology is well-defined.

$^{186}$Re isotope was chosen since it has the largest $(\gamma, n)$ cross section of all radioisotopes of interest [8], it can be used with a high specific activity for antibody and peptide radiolabelling [9] and for the preparation of phosphonates for bone pain palliation [10]. It is also possible to use the $^{186}$Re with a lower specific activity for intravascular radiotherapy for inhibition of coronary restenosis after angioplasty.

The other radioisotope investigated, $^{225}$Ra/$^{225}$Ac is a possible isotope produced with an actinide target. The application of $^{225}$Ac and, in particular, its daughter $^{213}$Bi in targeted alpha therapy is promising. These radioisotopes are usually used in combination with peptides with short uptake time and with antibodies seeking blood cancer cells. With a monoclonal antibody that interferes with the HER2/neu receptor, it has proved effectiveness in: leukemia, lymphoma, breast, ovarian, neuroblastoma and prostate cancers [11]. Currently, $^{225}$Ac is produced by decay of $^{225}$Ra ($^{235}$U chain) or by reaction $^{226}\mathrm{Ra}(n, 2n)^{225}\mathrm{Ra} \to {}^{225}\mathrm{Ac}$ and is available in very small amounts (about 1 Ci per year), which is very little compared to the need for large scale application. Thus, the investigation of the new production route on $^{225}$Ac isotope is also needed.

## 3. Results and discussions

We have developed a complex simulation code of the CBS between laser photons and relativistic electrons considering the electron beam size and emittance [12, 13], and a data-based Monte Carlo simulation program to predict the photonuclear reaction yield as well as to evaluate the subsequent specific activity of the radioisotopes [14]. By utilizing these codes, we simulated the CBS process to produce the $\gamma$ beam with the most appropriate parameters, its transport and delivery to the isotopic target for irradiation, and the subsequent radioisotopes production.

In the simulations, we considered cylindrical targets with different thicknesses and a $\gamma$-beam flux of $10^{11}$ s$^{-1}$, which is a conservative value for ELI–NP. The emittance of the $\gamma$ beam was chosen about 10 nm rad and the irradiation target was located approximately 9.6 m downstream of the laser–electron interaction point. While the solid oxide target of $^{100}\mathrm{MoO}_3$

with a density of 4.7 g/cm$^3$ was used for the production of $^{99}$Mo/$^{99m}$Tc, the metallic targets of $^{187}$Re and $^{226}$Ra with densities of 21.04 g/cm$^3$ and 5.0 g/cm$^3$ were used for $^{186}$Re and $^{225}$Ra/$^{225}$Ac, respectively.

The convolution between the $\gamma$-beam spectrum and the reaction cross section plays a key role in the production of the radioisotopes. We investigated the dependence of the saturation specific activity of the radioisotopes on the incident $\gamma$-ray energy. Figure 1 shows specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes produced by photonuclear reactions as a function of the incident $\gamma$-ray energy. It is found that for the given isotopic target dimension, the $\gamma$ beam with an end-point energy of 14.7 MeV, 13.8 MeV and 12.6 MeV could result in the highest specific activity for the $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac, respectively. We have used the optimized energy of the $\gamma$ beam in the Monte Carlo simulation presented below.

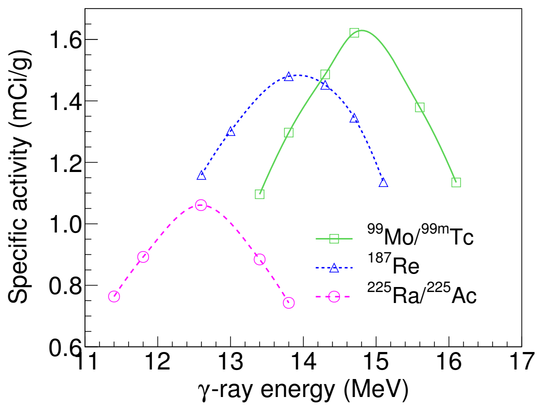


Fig. 1. Saturation specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes as a function of the incident $\gamma$-ray energy. The isotopic target with radius of 2.0 mm and thickness of 1.0 cm was used.

It was also interesting to optimize the isotopic target dimension, at defined irradiation time interval such to maximize the activities of the radioisotopes. Using an appropriate $\gamma$-beam energy shown in Fig. 1, we demonstrated in Fig. 2 the saturation specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes as a function of the target thickness. It is shown that the thinner the isotopic target, the higher the specific activity was. This is mainly caused by the attenuation effect of photons in the target material. Since the $^{187}$Re target had a higher density than the other two targets, $^{100}$MoO$_3$ and $^{226}$Ra, it led to a larger mass attenuation coefficient for a specified $\gamma$ beam irradiating on the target, the specific activity of the $^{186}$Re decreased more rapidly with the increase of the target thickness. It was also demonstrated in Fig. 2 that the highest specific activity of approximately 1.6 mCi/g for $^{99}$Mo/$^{99m}$Tc, 1.5 mCi/g for $^{186}$Re and 1.1 mCi/g for $^{225}$Ra/$^{225}$Ac can be achieved considering a thin target, *e.g.* radius 2.0 mm and thickness 1.0 cm.

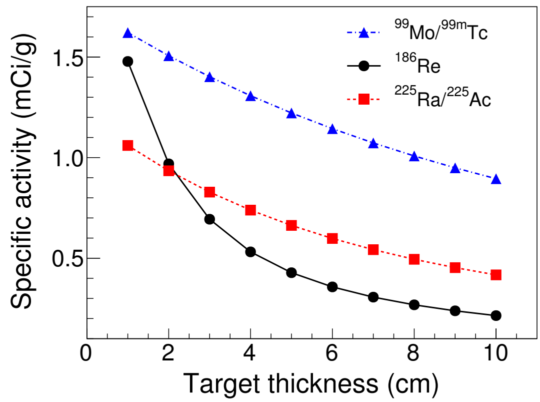


Fig. 2. Saturation specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes as a function of the target thickness. The calculations were performed at the optimal $\gamma$-beam energy and the isotopic target with radius of 2.0 mm was used.

The saturation specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes as a function of target radius was further calculated and shown in Fig. 3. According to our simulations, on the one hand, the $^{99}$Mo/$^{99m}$Tc case showed an interesting trend that the activity increased with a small quantity with the increase in the target radius until 1.0 mm and then de-

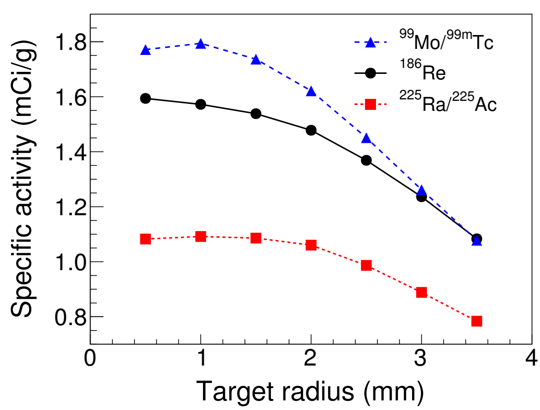


Fig. 3. Saturation specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac radioisotopes as a function of the target radius. The $\gamma$-beam profile was chosen 10 mm in diameter in order to cover the entire surface of the target. The isotopic target with thickness of 1.0 cm was used.

creased. On the other hand, the activity decreased from 2 mm radius for $^{225}$Ra/$^{225}$Ac, which was different from the $^{99}$Mo/$^{99m}$Tc and $^{186}$Re cases. These trends were attributed to the matching the CBS $\gamma$-beam spectrum with a peaked photonuclear cross section. By using an appropriate $\gamma$ beam, the target with a small radius provided a relatively high specific activity for these radioisotopes at which a good convolution between the $\gamma$-beam spectrum and the reaction cross section occurred.

Figure 4 shows the dependence of the specific activities of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac on the irradiation time integral. For the cases of $^{99}$Mo/$^{99m}$Tc and $^{225}$Ra/$^{225}$Ac, the generator radioisotopes $^{99}$Mo and $^{225}$Ra have larger half-life than those of their daughters $^{99m}$Tc and $^{225}$Ac, the radioactive decay equilibrium between them can be achieved after a long enough irradiation integral. Then, the daughter radioisotopes had almost the same activities with the generators (Fig. 4). Taking $^{99}$Mo/$^{99m}$Tc as an example and using an optimal $\gamma$-beam energy (14.7 MeV) and a thin target (radius 2 mm, thickness 1 cm), the specific activity of the $^{99}$Mo and $^{99m}$Tc radioisotopes reached 0.36 mCi/g and 0.24 mCi/g, respectively after one day irradiation, while their specific activities have a saturation value exceeding 1.6 mCi/g. In the production case of $^{186}$Re, the specific activity shown in Fig. 4 exceeded 0.25 mCi/g after one day irradiation and then reached 1.5 mCi/g after about 5–6 times half-life irradiation integral.

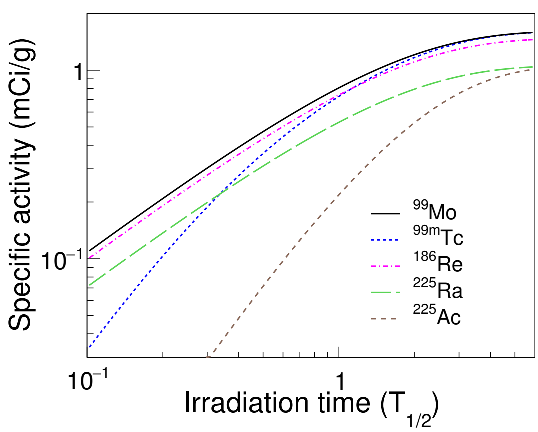


Fig. 4. Specific activity of $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac as a function of irradiation time integral. Here, $T_{1/2}$ represents the half-life of the radioisotopes $^{99}$Mo ($T_{1/2}$ = 2.8 day), $^{186}$Re ($T_{1/2}$ = 3.7 day) and $^{225}$Ra ($T_{1/2}$ = 14.8 day) produced by photonuclear reaction. The optimized $\gamma$-beam energy shown in Fig. 1 was used and the input parameters for the isotopic target were 2.0 mm radius and 1.0 cm thickness.

## 4. Conclusion

We have demonstrated the possibility of employing high-intensity $\gamma$ beams at ELI–NP for the photonuclear production of several relevant radioisotopes of medical interest, $^{99}$Mo/$^{99m}$Tc, $^{186}$Re and $^{225}$Ra/$^{225}$Ac. Using Monte Carlo simulations, we estimated that after a long enough irradiation integral, a specific activity of the order of 1–2 mCi/g can be achieved for a thin target (radius 1–2 mm, thickness 1 cm) considering a $\gamma$-beam flux of $10^{11}$ photons/s. Note that such $\gamma$ beam will be achieved in the first phase of operation of the ELI–NP facility. If the achieved $\gamma$-beam flux would be higher, the specific activities of radioisotopes can be easily scaled accordingly. We conclude that ELI–NP will present a great potential for the production of some key radioisotopes in sufficient quantities for nuclear medicine research.

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REFERENCES

[1] World Nuclear Association, Radioisotopes in Medicine, Information Library, Nov. 2014.

[2] D. Habs, U. Köster, *Appl. Phys. B* **103**, 501 (2011).

[3] V.N. Litvinenko *et al.*, *Phys. Rev. Lett.* **78**, 4569 (1997).

[4] W. Luo *et al.*, *Laser Part. Beams* **31**, 89 (2013).

[5] W. Luo *et al.*, *Appl. Phys. B: Lasers Opt.* **101**, 761 (2010).

[6] B. Szpunar *et al.*, *Nucl. Instrum. Methods A* **729**, 41 (2013).

[7] `http://www.eli-np.ro/(2015)`

[8] IAEA Nuclear data services, see `https://www-nds.iaea.org/exfor/exfor.htm`

[9] F.B. van Gog *et al.*, *J. Nucl. Med.* **37**, 352 (1996).

[10] J.M.S.P. Quirijnen *et al.*, *J. Nucl. Med.* **37**, 1511 (1996).

[11] A.M. Ballangrud *et al.*, *Clin. Cancer Res.* **10**, 4489 (2004).

[12] S. Agostinelli [Geant4 Collaboration], *Nucl. Instrum. Methods A* **506**, 250 (2003).

[13] D. Filipescu *et al.*, *AIP Conf. Proc.* **1645**, 322 (2015).

[14] W. Luo *et al.*, "Monte Carlo Simulation for Determining Photonuclear Production of Medical Isotopes Using Compton Scattering Gamma Beam", to be published.